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Risk factors for human herpesvirus 8 seropositivity in the AIDS Cancer Cohort Study

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Abstract

Background: Cigarette smoking has been associated with a decreased risk for AIDS-related and classical KS, but whether it is associated with decreased risk of human herpesvirus 8 (HHV-8) infection is unknown.
Study design: We evaluated factors associated with HHV-8 seropositivity in 2795 participants (132 with KS) in the National Cancer Institute AIDS Cancer Cohort, including 1621 men who have sex with men (MSM), 660 heterosexual men and 514 women. Odds ratios (OR) and 95% confidence intervals were estimated using logistic regression models.
Results: Among non-KS subjects, HHV-8 seropositivity was 6%, 13% and 29% among women, heterosexual men and MSM, respectively. HHV-8 seropositivity was decreased in heavier (≥1/2 pack/day) compared to lighter smokers among women (5% versus 8%; adjusted OR (aOR) 0.4; 95% CI 0.2–0.8) and MSM (27% versus 32%; aOR 0.7; 95% CI 0.6–1.0), but not among heterosexual men (12% versus 16%; aOR 0.7; 95% CI 0.4–1.2). HHV-8 seroprevalence was increased in heavier (≥1 drink/day) compared to lighter consumers of alcohol among women (16% versus 4%; adjusted OR 5.2; 95% CI 2.3–12), but not among MSM (33% versus 28%; aOR 1.2; 95% CI 0.9–1.6) or heterosexual men (13% versus 13%; aOR 1.1; 95% CI 0.6–2.0). In analyses adjusted for smoking and drinking, HHV-8 seropositivity was positively associated with chlamydia infection (OR = 4.3; 95% CI 1.2–13) and with marital status among women $p_{\text{heterogeneity}} = 0.03$, and with hepatitis (OR = 1.6; 95% CI 1.2–2.1), gonorrhea (OR = 1.5; 95% CI 1.1–1.9), genital warts (OR = 1.5; 95% CI 1.1–2.0) and nitrate inhalant use (OR = 1.7; 95% CI 1.3–2.3) among MSM.
Conclusions: Inverse association of HHV-8 seropositivity with cigarette smoking may indicate protective effect of tobacco smoke on HHV-8 infection, whereas positive associations with alcohol may reflect either behavioral factors or biological effects modulating susceptibility. Smoking and drinking may influence KS risk, at least in part, by altering the natural history of HHV-8 infection.

Keywords: Kaposi sarcoma; Transmission; Men who have sex with men; Injection drug use; United States

1. Introduction

Human herpesvirus 8 (HHV-8, also called Kaposi sarcoma-associated herpesvirus) is accepted as the infectious cause of Kaposi sarcoma (KS) (Boshoff and Weiss, 2001; Chang et al., 1994), the most common tumor among

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persons with AIDS (Frisch et al., 2001; Mbulaiteye et al., 2003b). HHV-8 seroprevalence is low (~3%) in the United States (Pellett et al., 2003) except among men who have sex with men (MSM; ~30%) who also have a high risk of AIDS-related KS (Martin et al., 1998). Seroprevalence is intermediate (5–10%) among HIV-positive heterosexual men, women and injection drug users (Lennette et al., 1996; Martin, 2003). HHV-8 seropositivity is variably associated, particularly among MSM, with sexual exposures, sexually transmitted disease (Martin et al., 1998), and injection and other drug use in some but not all studies (Renwick et al., 2002).

Cigarette smoking has been associated with decreased risks for AIDS-related KS in the U.S. (Hoover et al., 1993; Nawar et al., 2005) and classical KS in Italy (Goedert et al., 2002), suggesting that cigarette smoking may modulate the natural history of HHV-8 infection. However, findings were equivocal in two studies conducted in Uganda, where KS is more common but smoking is less prevalent (Ziegler et al., 2003, 1997). Whether cigarette smoking decreases the risk of HHV-8 infection is unknown. We therefore evaluated the association of various behavioral factors, including cigarette smoking, with HHV-8 seropositivity among persons with AIDS in the U.S.

2. Methods

2.1. Study population and serology methods

We studied 2795 patients with AIDS aged ≥18 years old participating in the National Cancer Institute's AIDS Cancer Cohort (NCI-ACC) study. The patients were enrolled at 24 AIDS treatment and clinical trial sites in the United States from October 1997 to January 2000. All patients met Centers the Disease Control and Prevention (CDC) criteria for AIDS diagnosis (1992). At enrollment, the median (inter-quartile range) CD4 lymphocyte count was 204 (82–281) cells/μL and HIV viral load was 32,759 (3315–156,084) copies/μL.

Interviewers used a Computer Assisted Personal Interview (CAPI) to obtain information on age, income, education, sexual behaviors, past medical history, lifetime use of cigarettes, alcoholic drink consumption in the past 12 months and use of recreational drugs in the past 12 months. Participants also gave a venous blood sample for HHV-8 testing. We tested for anti-HHV-8 antibodies using an enzyme-linked immunosorbent assay directed against the K8.1 glycoprotein antigen, as previously described (Engels et al., 2000; Mbulaiteye et al., 2003a). Ethical approval to conduct the study was granted by institutional review boards at the National Cancer Institute and at collaborating institutions.

2.2. Statistical methods

We performed analyses of HHV-8 seropositivity separately for women ($n = 514$), heterosexual men ($n = 660$) and MSM ($n = 1621$). Eight additional subjects with inadequate samples ($n = 7$) or incomplete data ($n = 1$) were excluded. Men were classified as MSM if they reported having ever had sexual contact with men and as heterosexual otherwise. Subjects with KS at or before enrollment were excluded from analyses evaluating associations with asymptomatic HHV-8 seropositivity.

We determined the crude and adjusted odds ratios (OR) of associations with HHV-8 seropositivity and associated 95% confidence intervals using logistic regression models. We specifically evaluated the relationship between cigarette smoking and HHV-8 seropositivity because prior studies have indicated an inverse association between cigarette smoking and KS (Hoover et al., 1993; Nawar et al., 2005). However, because cigarette smoking and alcohol consumption tend to track together, we examined the association between these variables among HHV-8 seronegative subjects using frequency tables to determine if they fulfilled the definition of a classical confounder (i.e., associated with each other and also with the disease outcome, in this case, HHV-8 seropositivity) (Hauck et al., 1991). In our data, cigarette smoking and alcohol consumption were associated. Thus, we controlled for alcohol consumption in the models estimating the independent association of cigarette smoking with HHV-8 seropositivity. Our primary multivariable model included cigarette smoking and alcohol consumption. To identify other variables that were significant predictors of HHV-8 seropositivity, we added all variables associated with HHV-8 seropositivity at $p < 0.10$ to the multivariable logistic models and determined the independent contribution of each individual variable to the full model using a stepwise procedure, with a $p \leq 0.05$ based on the likelihood ratio test used as the stay or enter criteria. Because our analysis was primarily for hypothesis generation, we did not adjust for multiple comparisons.

3. Results

One hundred thirty two (4.7%) of the subjects had KS at or before enrollment, including 2 women, 6 heterosexual men and 124 MSM (Table 1). One hundred nine (83%) of the subjects with KS had HHV-8 antibodies, including both of the women, three of the six heterosexual men and 104 of the 124 MSM. Associations with asymptomatic HHV-8 seropositivity were evaluated among the 2663 subjects without KS, of whom 554 (21%) had HHV-8 antibodies.

3.1. HHV-8 seropositivity among women

HHV-8 antibodies were detected among 6% of the women without KS. In univariate analyses, seropositivity was not significantly associated with age, race or income (Table 2). Women who had never married were more likely to be HHV-8 seropositive as compared to women who were divorced, separated or widowed. Women with less than 12 years of education were more likely to be seropositive compared to

Table 1
Percent distribution of demographic, medical and behavioral characteristics of subjects with or without KS, AIDS Cancer Cohort Study, 1997–2000

Characteristics	Women ($n = 514$) %	Heterosexual men ($n = 660$) %	MSM ($n = 1621$) %
Age group (years)			
<30	11	3	4
30–39	46	30	44
40–49	35	48	38
>50	8	19	14
Race/ethnicity			
Non-Hispanic white	24	15	60
Non-Hispanic black	65	72	30
Hispanic	10	9	8
Other	1	2	2
Marital status			
Never married	39	38	64
Married/living with partner	20	23	20
Divorced/separated/widowed	41	38	16
Income (US$)			
<15,000	78	78	55
15,000–29,999	15	14	20
30,000 or more	6	7	24
Education			
<12 Years	37	39	11
High school graduate	31	29	22
College/vocational school	27	28	43
Post graduate	4	3	16
History of			
Mononucleosis	4	1	10
Hepatitis	24	38	38
Gonorrhea	38	48	48
Syphilis	17	17	25
Chlamydia	25	–	–
Genital herpes	29	19	24
Genital warts	22	9	24
Blood transfusion	33	28	23
Nitrate inhalants (ever use)	7	14	67
Injection drugs (ever use)	28	41	16
Crack cocaine (past 12 months)	24	23	13
Heroin (past 12 months)	9	13	2
Sexual activity (past 12 months)	61	65	72
KS	0.4	1	8
Cigarettes smoked per day (lifetime)			
≥1/2 Pack	55	69	60
Alcohol consumption per day (past 12 months)			
≥1 Drink	16	20	19

women who had some college level education. A history of chlamydia infection, but not of other sexually transmitted diseases, was marginally associated with HHV-8 seropositivity. Use of crack cocaine or heroin within the past 12 months, but not of nitrate inhalants or injection drugs, was significantly associated with seropositivity (Table 2).

Slightly more than two-thirds of the women had ever smoked cigarettes and 62% had consumed alcohol in the past 12 months. Among HHV-8 seronegative women, those who had ever smoked cigarettes were more likely than those who had not to report alcohol consumption (65% versus 48%, $p < 0.001$). In univariate analyses, HHV-8 seropositivity was lower among women who smoked more than one-half pack of cigarettes per day compared to women who smoked less (5% versus 8%, $p = 0.13$; Table 2). Conversely, HHV-8 seropositivity was higher among women who consumed more than one alcoholic drink per day in the past 12 months compared to women who drank less (16% versus 4%, $p < 0.001$). Inverse HHV-8 associations with smoking became statistically significant in analyses that adjusted for the effects of alcohol consumption ($p = 0.02$; Table 3). Likewise, the positive HHV-8 associations with alcohol consumption became accentuated by adjustment for the effects of smoking ($p < 0.001$). In analyses that adjusted for effects of smoking and alcohol consumption, chlamydia infection in the past 12 months was significantly associated with HHV-8 seropositivity (OR = 4.3;

Table 2
Prevalence and crude odds ratios of HHV-8 seropositivity for selected demographic, medical and behavioral characteristics of subjects without KS, AIDS Cancer Cohort Study, 1997–2000

Characteristics	Women ($n = 512$)		Heterosexual men ($n = 654$)		MSM ($n = 1497$)	
	% HHV-8+	OR (95% CI)[a]	% HHV-8+	OR (95% CI)	% HHV-8+	OR (95% CI)
Age group (years)						
<30	9	Reference	11	Reference	26	Reference
30–39	5	0.5 (0.2–1.6)	12	1.1 (0.2–5.2)	27	1.0 (0.6–1.8)
40–49	7	0.8 (0.3–2.4)	11	1.0 (0.2–4.5)	31	1.3 (0.7–2.2)
>50	5	0.5 (0.1–2.9)	22	2.3 (0.5–11)	32	1.3 (0.7–2.5)
p-Value for trend		0.91		0.04		0.07
Race/ethnicity						
Non-Hispanic white	4	Reference	11	Reference	30	Reference
Non-Hispanic black	7	1.8 (0.7–4.9)	13	1.2 (0.7–2.3)	25	0.8 (0.6–1.0)
Hispanic	4	0.9 (0.2–4.9)	16	1.5 (0.6–3.7)	40	1.6 (1.1–2.4)
Other	0	0	25	2.7 (0.5–15)	46	2.0 (0.9–4.5)
p-Value for heterogeneity		0.32		0.67		0.002
Income (US$)						
<15,000	6	Reference	12	Reference	27	Reference
15,000–29,999	6	1.1 (0.4–2.8)	13	1.0 (0.5–2.0)	32	1.3 (1.0–1.7)
30,000 or more	3	0.5 (0.1–3.8)	20	1.8 (0.9–3.8)	31	1.2 (0.9–1.5)
p-Value for trend		0.63		0.17		0.16
Marital status						
Never married	10	Reference	11	Reference	30	Reference
Married/living with partner	4	0.4 (0.1–1.1)	13	1.3 (0.7–2.4)	29	0.9 (0.7–1.3)
Divorced/separated/widowed	3	0.3 (0.1–0.8)	17	1.7 (1.0–2.9)	26	0.8 (0.6–1.1)
p-Value for heterogeneity		<0.01		0.12		0.37
Education						
<12 Years	8	Reference	14	Reference	21	Reference
High school graduate	8	1.0 (0.4–2.1)	11	0.7 (0.4–1.3)	28	1.5 (0.9–2.3)
College/vocational school	2	0.3 (0.1–0.9)	15	1.1 (0.6–1.9)	28	1.5 (1.0–2.3)
Post graduate	4	0.5 (0.1–4.2)	23	1.8 (0.6–5.3)	35	2.0 (1.3–3.2)
p-Value for trend		0.05		0.48		0.005
History of						
Mononucleosis	0	0	25	2.2 (0.4–11)	33	1.2 (0.9–1.8)
p-Value				0.35		0.25
Hepatitis	6	0.9 (0.9–2.2)	13	0.9 (0.6–1.5)	36	1.7 (1.3–2.1)
p-Value		0.86		0.71		<0.001
Gonorrhea	5	0.6 (0.3–1.4)	12	0.8 (0.5–1.3)	35	1.7 (1.3–2.1)
p-Value		0.26		0.36		<0.001
Syphilis	9	1.7 (0.7–3.9)	12	0.9 (0.5–1.6)	34	1.4 (1.1–1.8)
p-Value		0.22		0.63		0.009
Chlamydia	7	3.2 (1.0–11)	–	–	–	–
p-Value		0.06				
Genital herpes	6	0.9 (0.4–2.0)	12	0.9 (0.5–1.6)	31	1.2 (0.9–1.5
p-Value		0.71		0.62		0.28
Genital warts	8	1.5 (0.7–3.4)	13	1.0 (0.4–2.1)	38	1.7 (1.3–2.1)
p-Value		0.31		0.93		<0.001
Blood transfusion	5	0.7 (0.3–1.6)	15	1.2 (0.7–1.9)	27	0.9 (0.7–1.2)
p-Value		0.37		0.57		0.35
Nitrate inhalants (ever use)	3	0.4 (0.1–3.1)	10	0.7 (0.3–1.4)	34	2.0 (1.5–2.5)
p-Value		0.39		0.27		<0.001
Injection drugs (ever use)	8	1.6 (0.8–3.5)	13	0.9 (0.6–1.5)	35	1.4 (1.0–1.9)
p-Value		0.20		0.75		0.02
Crack cocaine (past 12 months)	11	3.6 (1.5–8.4)	13	0.9 (0.5–1.5)	31	1.2 (0.8–1.6)
p-value		0.003		0.64		0.38

Table 2 (*Continued*)

Characteristics	Women ($n = 512$)		Heterosexual men ($n = 654$)		MSM ($n = 1497$)	
	% HHV-8+	OR (95% CI)[a]	% HHV-8+	OR (95% CI)	% HHV-8+	OR (95% CI)
Heroin (past 12 months)	13	2.8 (1.0–7.5)	15	1.1 (0.6–2.0)	21	0.6 (0.3–1.4)
p-Value		0.04		0.87		0.24
Sexual activity (past 12 months)	7	1.8 (0.8–4.3)	12	0.6 (0.4–1.0)	31	1.4 (1.1–1.9)
p-Value		0.17		0.06		0.005
Cigarettes smoked per day (lifetime)						
<1/2 Pack	8	Reference	16	Reference	32	Reference
≥1/2 Pack	5	0.56 (0.27–1.18)	12	0.73 (0.45–1.17)	27	0.78 (0.62–0.98)
p-Value		0.13		0.19		0.03
Alcohol consumption per day (past 12 months)						
<1 Drink	4	Reference	13	Reference:	28	Reference
≥1 Drinks	16	4.5 (2.1–9.5)	13	1 (0.6–1.7)	33	1.3 (1.0–1.9)
p-Value		<0.001		0.99		0.10

[a] OR, crude odds ratio; CI, confidence interval.

95% CI 1.2–13). Women who were divorced, separated or widowed were less likely to be HHV-8 seropositive as compared to never married women (Table 3).

3.2. HHV-8 seropositivity among heterosexual men

HHV-8 antibodies were detected among 13% of heterosexual men without KS, twice the prevalence among women ($p < 0.001$). In univariate analyses, HHV-8 seropositivity was two-fold higher among heterosexual men aged 50 years or older compared to prevalence in younger men. HHV-8 seropositivity was unrelated to race, income or history of sexually transmitted diseases. Compared to heterosexual men who had never been married, those who were divorced, separated or widowed had a marginally elevated prevalence of HHV-8 seropositivity ($p = 0.12$; Table 2).

Eighty-three percent of heterosexual men had ever smoked cigarettes and 67% had consumed alcohol in the past year. Among HHV-8 seronegative heterosexual men, those who had ever smoked cigarettes were marginally more likely than those who had not to report alcohol consumption (68% versus 59%, $p < 0.10$). HHV-8 seropositivity was slightly decreased among smokers (12% versus 16%, $p = 0.19$); however, that association was not statistically significant, even with adjustment for alcohol drinking ($p = 0.18$). HHV-8 seropositivity was unrelated to alcohol consumption and was slightly decreased among men reporting sexual activity in the past 12 months (Table 2), but the latter difference was not significant in adjusted models.

3.3. HHV-8 seropositivity among MSM

HHV-8 seropositivity was 29% among MSM without KS, more than double the prevalence among heterosexual men and more than four times the prevalence among women (all $p < 0.001$). In univariate analyses, seropositivity among MSM was positively associated with older age, Hispanic ethnicity, higher educational attainment, sexual activity in the past 12 months and history of hepatitis, syphilis, gonorrhea and genital warts (Table 2). The use of nitrate inhalants and injection drugs, but not crack cocaine or heroin, in the past 12 months was significantly associated with HHV-8 seropositivity (Table 2).

Seventy-one percent of MSM had ever smoked cigarettes and 80% had consumed alcohol in the 12 months. Among HHV-8 seronegative MSM, those who had ever smoked cigarettes reported similar frequency of alcohol consumption as those who had never smoked cigarettes (79% versus 75%, $p < 0.19$). HHV-8 seropositivity was significantly decreased among MSM who were heavier smokers compared to MSM who were lighter smokers (27% versus 32%; $p = 0.03$, Table 2). However, the prevalence of HHV-8 seropositivity among MSM did not significantly differ according to alcohol consumption (33% versus 28%; $p = 0.1$; Table 2). Nonetheless, in analyses adjusting the effects of one for the other, the statistical significance of the HHV-8 associations with cigarette smoking was accentuated ($p = 0.02$). In multivariable models, HHV-8 seropositivity was significantly associated with smoking, history of hepatitis, gonorrhea, genital warts and nitrate inhalant use, but not with sexual activity, injection drug, heroin, crack cocaine use or alcohol consumption (Table 3).

HHV-8 seropositivity among MSM light and heavier smokers with KS was similar (84% versus 83%).

4. Discussion

In the NCI-ACC study, HHV-8 seropositivity was inversely associated with cigarette smoking and positively associated with alcohol consumption among women and MSM. The associations, particularly among women, were independent of sexual and recreational drug exposures. The magnitudes of the associations between cigarette smoking and alcohol consumption with HHV-8 seropositivity were accentuated in analyses that adjusted one for the other, indi-

Table 3
Adjusted odds ratios for associations between HHV-8 seropositivity and demographic, medical and behavioral characteristics among subjects without KS, AIDS Cancer Cohort Study 1997–2000

Characteristics	Women[a] ($n = 512$)		Heterosexual men[a] ($n = 654$)		MSM[a] ($n = 1497$)	
	aOR	95% CI	aOR	95% CI	aOR	95% CI
Age group (years)	NA				NA	
<30			Reference			
30–39			1.1	0.2–5.1		
40–49			1.0	0.2–4.6		
>50			2.4	0.5–11		
p-Value for heterogeneity				0.02		
Race/ethnicity	NA		NA			
Non-Hispanic white					Reference	
Non-Hispanic black					0.9	0.7–1.2
Hispanic					1.6	1.0–2.4
Other					2.5	1.1–5.7
p-Value for heterogeneity						0.03
Marital status			NA		NA	
Never married	Reference					
Married/living with partner	0.4	0.1–1.3				
Divorced/separated/widowed	0.3	0.1–0.8				
p-Value for heterogeneity		0.03				
History of						
Hepatitis	NA		NA		1.6	1.2–2.1
p-Value						0.002
Gonorrhea	NA		NA		1.5	1.1–1.9
p-Value						<0.001
Chlamydia (past 12 months)	4.3	1.2–13	NA		NA	
p-Value		0.007				
Genital warts	NA		NA		1.5	1.1–2.0
p-Value						0.004
Nitrate inhalants (ever use)	NA				1.7	1.3–2.3
p-Value						0.001
Cigarettes smoked per day (lifetime)						
<1/2 Pack	Reference					
≥1/2 Pack	0.4	0.2–0.8	0.7	0.4–1.2	0.7	0.6–1.0
p-Value for heterogeneity		0.02		0.20		0.02
Alcohol consumption per day (past 12 months)						
<1 Drink	Reference					
≥1 Drink	5.2	2.3–12	1.1	0.6–2.0	1.2	0.9–1.6
p-Value for heterogeneity		<0.001		0.69		0.12

NA: not applicable; aOR: adjusted odds ratio; CI: confidence interval.

[a] Final model includes: marital status, chlamydia infection, smoking and alcohol consumption for women; age group, smoking and alcohol consumption for heterosexual men; and history of hepatitis, gonorrhea, genital warts, nitrate inhalant use and smoking, alcohol consumption for MSM (see Section 2.2). For each population group, estimates are given for variables that contributed significantly ($p < 0.05$) to the primary model including alcohol consumption and cigarette smoking were retained.

cating negative confounding. The associations were qualitatively similar among heterosexual men, but not statistically significant, perhaps because of confounding with unreported homosexual sexual activity.

The inverse association between cigarette smoking and HHV-8 seropositivity is interesting because inverse associations have been previously reported between cigarette smoking and AIDS-related KS in the U.S. (Hoover et al., 1993; Nawar et al., 2005) and classical KS in Italy (Goedert et al., 2002). In the U.S. Multicenter AIDS Cohort study, persons who smoked at least one-half pack of cigarettes per day experienced half the incidence of AIDS-related KS as compared to that in non-smokers (Hoover et al., 1993). That study was unable to distinguish the effects of cigarette smoking on the risk of HHV-8 infection from those on KS risk in HHV-8 infected individuals. In the NCI-ACC study (Nawar et al., 2005), Nawar et al. observed an inverse association between KS and cigarette smoking in an analysis restricted to HHV-8 seropositive MSM with AIDS. In Italy, patients with classical KS were one-fourth as likely to be current or former smokers as compared to HHV-8 seropositive controls (Goedert et al., 2002). Together,

these studies suggest that smoking may decrease the risk of KS among HHV-8 seropositive persons, perhaps through action of components of tobacco smoke. However, two studies conducted in Uganda, where KS is relatively common (Ziegler et al., 2003, 1997) produced equivocal results. In one, an inverse association between endemic KS and current or prior smoking was reported in a case–control analysis of HIV-seronegative subjects with cancer, but those results were not statistically significant (Ziegler et al., 2003). In the other, smoking was unrelated to AIDS-related KS (Ziegler et al., 1997). The results from these studies two studies are inconclusive because smoking-associated cancers were not excluded from the analyses and because the prevalence of smoking is low in Uganda (approximately 20% among controls and cases), which reduced their statistical power.

Our findings of inverse associations between HHV-8 seropositivity and cigarette smoking are intriguing. Similar findings have been reported by Baeten et al. who observed a lower HHV-8 seroprevalence among Kenyan truck drivers who smoked compared to those who did not (Baeten et al., 2002). The observation of similar findings among the people who have different AIDS- and, most likely, HHV-8-risk profiles, may be interpreted as indicative of a specific biologic effect of smoking on HHV-8 seropositivity. Although smoking may decrease HHV-8 seropositivity by masking the humoral immune response to HHV-8, this explanation is not supported by our observation that HHV-8 seroprevalence was similar among MSM with KS who did and did not smoke. Instead, we speculate that components in tobacco smoke could modulate HHV-8 infection through their effects on leucocytosis (Smith et al., 2003), secretion of oxygen radicals (Sopori, 2002) and T helper 1 (T_H1)/T_H2 cytokine balance (Leow and Maibach, 1998).

Our finding of a positive association between alcohol consumption and HHV-8 seropositivity among the women is interesting. A similar finding was reported in a study of female commercial sex workers in Kenya, where current or past consumers of alcohol had significantly higher HHV-8 seropositivity compared to alcohol abstainers (Lavreys et al., 2003). However, HHV-8 seropositivity was unrelated to alcohol consumption in the study of Kenyan truck drivers (Baeten et al., 2002) and in the study of Ugandan HIV-negative cancer patients (Ziegler et al., 2003), suggesting that this relationship is complex. Because alcohol consumption is associated with diverse adverse biological effects, e.g., on lymphocyte subpopulations, T_H1/T_H-2 cytokine balance and nutrition (Isaki and Kresina, 2000), it is conceivable that alcohol consumption could increase the risk of HHV-8 infection. Moreover, the potent behavioral modification associated with alcohol consumption may also influence the probability of exposure to HHV-8.

The strengths of our study include access to a well-characterized cohort of AIDS patients who have diverse risk factors for HIV and HHV-8 infection. This allowed us to compare and contrast the epidemiology of HHV-8 in different populations. Our findings among women are particularly informative because they would not be confounded by unreported male homosexual exposures. Furthermore, because we had detailed drug and sexual exposure data, we were able to control for the effects of these exposures when estimating HHV-8 associations with smoking and alcohol consumption. Finally, recall bias is unlikely to explain our findings because all participants had AIDS at enrollment and were unaware of their HHV-8 serostatus.

Nonetheless, some limitations should be considered. Available HHV-8 serological assays are imperfect (Rabkin et al., 1998). In our study, HHV-8 serology identified less than 100% of subjects with KS, a group thought to be universally HHV-8 infected, suggesting misclassification bias remains possible. Even so, misclassification of serostatus among subjects without KS would likely have been non-differential, which would bias our results toward the null. We performed multiple statistical comparisons; readers should interpret our results with caution. Other limitations include using cross-sectional data, which does not allow temporality to be determined. Moreover, we relied on self-reported behavioral data that likely over-simplified complex patterns of behavior, which tend to vary with time. Finally, it is possible that smoking exposure status may have been misclassified for participants who modified this behavior following the diagnosis of AIDS or KS.

To conclude, our findings suggest that cigarette smoking is associated with lower risk and alcohol consumption with higher risk of HHV-8 infection. Identification of components in cigarette smoke protective against HHV-8 infection and/or KS may provide insight into pathogenesis and, potentially, novel approaches for prevention. Confirmation of HHV-8 associations with alcohol consumption would justify public health messages informing people with AIDS about this potentially serious adverse effect.

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Appendix A

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